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Procedia Engineering 148 (2016) 1320 – 1325

Procedia Engineering

www.elsevier.com/locate/procedia

4th International Conference on Process Engineering and Advanced Materials

The Effect of Co-solvent on the Solubility of a Sparingly Soluble Crystal of Benzoic Acid

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Abstract

The Benzoic acid is widely used in the pharmaceutical industry, plasticizers and food preservative which show low aqueous solubility and dissolution rate. The investigation has been made to improve the solubility of benzoic acid by using co-solvent. The co-solvent solution is prepared by using glycerol in water by volume ratio. The result shows the relation between solubility in different co-solvent and temperature whereby as the percentage of glycerol increase, the solubility of benzoic acid increase. A similartrend was depicted in term of solubility relation with temperature as the temperature increase amount of benzoic acid dissolved also increase. Thermodynamics dissociation constant, pK_a are directly proportional totemperature between 30°C and 90°C. Enthalpy and entropy change of the dissociation process are 2.907 kJ/mole and -24.09 J/mole respectively. Gibbs free energy of dissociation at 30°C, 60°C and 90°C are -4.390 KJ/mole, -5.114 KJ/mole and 5.837 KJ/mole respectively depicted that the solubility increased with temperature.

Peer-review under responsibility of the organizing committee of ICPEAM 2016

Keywords: Solubility; Co-solvent; Benzoic Acid; Sparingly Soluble; Glycerol

1. Introduction

Crystallization is natural or manufactured phenomenon in the development of solid crystals that deposit from a solution or precipitating directly from gas. Crystallization plays an important role in the various field of research such as pharmaceuticals, physics, chemistry, food science, biological science and etc [1, 2, 3, 4]. Benzoic acid ($C_7H_6O_2$) is a colorless crystalline solid, which is widely used as an important intermediate for the preparation of many other organic substances applied in the fields of pharmaceuticals, resins, plasticizers, dyes, cosmetics and preservatives [5, 6]. It is used as an intermediate in the biosynthesis of various secondary metabolites as well in the preparation of cosmetics, resins, dyes, and pharmaceutical industries [7]. Its salts are mainly used as food preservatives, fats, and fruit juices. Industrially, it is obtained as a by-product during the liquid phase oxidation of toluene with air as an oxidant and acetic acid as solvent. Therefore, knowledge of the solubility of benzoic acid in solvents as well as a reactant is important for making the reaction mixture homogeneous and also for separations. Solubility, in quantitative, is term as the concentration of solute in a saturated solution at a certain temperature [8,9]. It is also defined as the spontaneous interaction of two or more substance to form a homogeneous molecular dispersion. Although major of the solute follows the solubility principal, it was found that some solute decrease solubility in increasing of temperature. The crystal solubility may be expressed as amolality, percentage, parts, molarity, volume fraction, and mole fraction. Benzoic acid is an aromatic carboxylic acid. It contains an aromatic ring or a benzene ring and one hydroxyl group attached to its carbon. The benzene ring has a hydrophobic characteristic, which tends to be non-polar and not soluble in water. The reason why benzoic

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1877-7058
Peer-review under responsibility of the organizing committee of ICPEAM 2016
doi:10.1016/j.proeng.2016.06.548

acid is considered to be sparingly soluble in the first place is because of its ability to form hydrogen bonding with water [10,11,12]. Water also consist a hydroxyl group and as the principle like dissolve like imply, meaning there is hydrogen bonding between benzoic acid and water. But due to the benzene ring, it makes the benzoic acid less soluble. The enhancement of solubility of benzoic acid (BA) is becoming more important thus the study of the solubility is relevant. A number of methodologies can be adapted to improve solubility of benzoic acid. A few methods established in the study of increasing solubility of sparingly soluble drugs, including the use of co-solvents, surfactants, organics and hydrophilic macromolecules, complexation, emulsion, liposomes, particle size reduction, solid dispersion, micronization, chemical modification, pH adjustment and others [1]. In the determination of a compound solubility, there are a few factors that affect the solubility, such as temperature, pressure, particle size, sonication, ionic strength and impurities [13,14]. The solubility depends on the polarity of the solute and solvent. In general, a polar solute dissolves in a polar solvent where the solubility of a polar solute is relatively low or insoluble in a non-polar solvent. Solubility increases with the increasing temperature, but it may not be necessary in all cases. For the endothermic process, as the temperature increase solubility also increase and vice versa while the process is exothermic [15]. In the case of pressure, the effect on solids and liquids are generally negligible and only significant in affecting the solubility of gaseous in liquid. As the pressure increase, the solubility of gasses in liquid also increases. The characteristic of the solute plays important rules in dissolution. In summary, solubility is affected by numbers of factors, whereby manipulating the factors would give either positive or negative impact on concentration dissolve. Due to the highly demand of the solubility data of benzoic acid in the pharmaceutical, food and other industry, many research efforts have been applied in overcoming the low solubility of benzoic acid . Many types of co-solvent can be used such as polyethylene glycol (PEG), glycerin, and ethanol [16]. Sparingly soluble salt is known to be less soluble in water, but in many cases, their solubility increase when toreact with water and its co-solvent. Several studies have investigated the solubility of benzoic acid in (acetic acid + water) binary mixtures. There is a scope to explore the effect of glycerol as co-solvent (glycerol + water) in enhancing the solubility of benzoic acid that has not been investigated in details yet. Therefore, the objective of this research is to study the effect of glycerol as co-solvents on the solubility at various temperatures.

2. Methodology

2.1 Materials

Analytical reagent grade benzoic acid (BA) with purity of 99.5% by mass was used in thewhole investigation and 99% Glycerol by volume was used as co-solvent compositions. The solvent contains with glycerol and distilled water.

2.2 Experimental procedure

Benzoic acid solubility in different percentage of glycerol was investigated using a static analytical method and the saturated solution composition was determined using thegravimetric method. Preparation of 500 ml of solvent was prepared by mixing a certain amount of glycerol (in percent) and water (balance amount) together at the desired temperature. An excess amount of benzoic acid was weighed and placed in the solvent solution. The solution was left to stir continuously for at least 3 hours. Different dissolution time was tested and the result shows 3 hours was enough time for benzoic acid to achieve saturation in all percentage of co-solvent. After the continuous stir, the solution was kept still for 1 hour to let the undissolved particle settle down in the lower level of the equilibrium solution. Once the gravitational settling was completed, 3 ml of clear solution was immediately taken out into a previously weighed vial using a pre-heated syringe. The vial was weighed again to identify the mass of the sample. The vial is placed in a dryer for 24 hours at 303 K to evaporateall the solvent of the solution. Once the drying process was done, the vial together with the remaining solutes was weighed again. The vial was weighed repeatedly until a constant weight of the vile was achieved. The solubility of benzoic acid was calculated in term of molality. The solubility data was measured at 10% increment of co-solvent with 15 K increment of temperature from 303.15 K to 363.15 K.

3. Result and Discussion

3.1 Co-solvent effect on Solubility of Benzoic acid(BA)

The effect of co-solvent on the solubility and the apparent dissociation constant (*Kc*) of benzoic acid at 30^{o}C was investigated at ten different percent of glycerol in the range of 0-90% glycerol. Figure 1 shows the molality of benzoic acid dissolve in the water-glycerol solvent. The graph plotted between the molality versus the percentage of glycerol in water shows an upward trend, increase in molality as the percentage of glycerol added increase. In every set of temperature that has been tested, it shows a steady increment of 0% of glycerol to 70% of glycerol, whereby from 70% to 90%, shows a significant increment in molality. Thus, as the percentage of glycerol added increase, the solubility of benzoic acid also increase.The solubility of Benzoic acid is well known to be sparingly soluble in water. From another study, the effect of adding another solvent into the primary solvent will enhance the solvent power thus increase in solubility. The benzene ring has a hydrophobic characteristic, which tends to be non-polar and not soluble in water.The reason why benzoic acid is considered to be sparingly soluble in the first place is because of its ability to form hydrogen bonding with water. Water also consist a hydroxyl group and there is hydrogen bonding between benzoic acid and water. Due to thebenzene ring, it makes the benzoic acid less soluble.In term of solubility, glycerol is easily dissolved in water because, it consist three hydroxyl group attached to each carbon, making more hydrogen bonding. From the mixing of both solvent, theamount of hydroxyl group increase, therefore, ahigher amount of benzoic acid could undergo hydrogen bonding, thus as the amount of glycerol increase, the solubility of benzoic acid also increases.

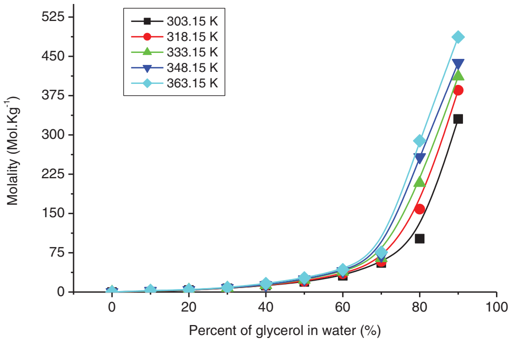


Figure 1: Effect of co-solvent on the solubility of benzoic acid

Apparent dissociation constant (*Kc*) of benzoic acid was determined using the modulated expression below for each solution [8];

$$K_c = \frac{10^{-pH}}{(y - 10^{-pH})} \quad (1)$$

Where,*y* is the total molar solubility of benzoic acid in solution. Table 1 contains values of *y*, 10^{-pH}, *Kc*, and percent of glycerol for each benzoic acid solution at 30°C, 60°C and 90°C.

Table 1: Benzoic acid dissociation constant and solubility at different temperature

At temperature 30°C						
percent of glycerol, I	Volume of benzoic acid	Concentration of benzoic acid, y	$\sqrt{I}$	pH	Log Kc	Kc
0.1	3.977165354	0.007105741	0.316227766	4.88	-2.7308	0.001859
0.3	4.237322835	7.18266028	0.547722558	5.15	-6.00628	9.86E-07
0.5	7.95480315	19.23042166	0.707106781	5.41	-6.69399	2.02E-07
0.7	8.362362205	55.47995346	0.836660027	5.68	-7.42414	3.77E-08
0.9	7.903937008	330.4944826	0.948683298	5.88	-8.39916	3.99E-09
At temperature 60°C						
percent of glycerol, I	Volume of benzoic acid	Concentration of benzoic acid, y	$\sqrt{I}$	pH	Log Kc	Kc
0.1	6.339370079	1.825782266	0.316227766	4.91	-5.17145	6.74E-06
0.3	12.67385827	7.650396669	0.547722558	5.18	-6.06368	8.64E-07
0.5	15.86598425	23.21859029	0.707106781	5.45	-6.81584	1.53E-07
0.7	24.43503937	64.63671268	0.836660027	5.73	-7.54048	2.88E-08
0.9	26.24094488	411.4008254	0.948683298	5.93	-8.54427	2.86E-09
At temperature 90°C						
percent of glycerol, I	Volume of benzoic acid	Concentration of benzoic acid, y	$\sqrt{I}$	pH	Log Kc	Kc
0.1	27.11622047	2.806034287	0.316227766	4.95	-5.39809	4E-06
0.3	58.07188976	8.367238062	0.547722558	5.22	-6.14258	7.2E-07

0.5	89.13070866	26.87870648	0.707106781	5.47	-6.89941	1.26E-07
0.7	77.23188976	75.96290159	0.836660027	5.79	-7.6706	2.14E-08
0.9	56.98937008	486.8085476	0.948683298	6.01	-8.69736	2.01E-09

A relation between apparent and thermodynamics dissociation constant for aqueous solutions at 30˚C

$$logK_a + 1.03\sqrt{I} = logK_c \quad (2)$$

Figure 2 shows the plot oflogK_c versuspercent of glycerol (I). Linear least-square analysis of the data at 30°C finds the thermodynamic dissociation constant K_a of benzoic acid. The calculated value of logK_a from the plot is -3.98 ± 0.043. The inverse of the predicted value corresponds thermodynamic dissociation constant,pK_a of benzoic acid at 30°C which is agreed with theliterature [9].

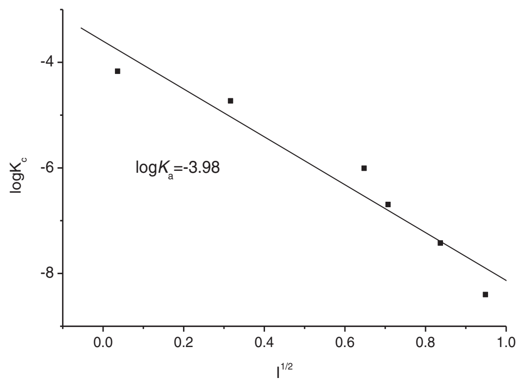
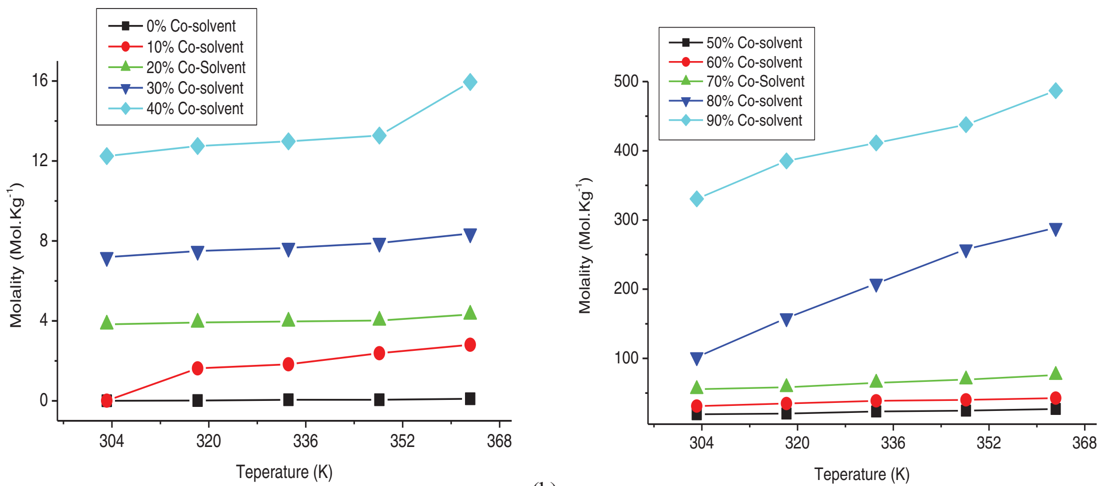


Figure 2: Thermodynamic dissociation constant of benzoic acid with co-solvents

3.2 Temperature effect on Solubility of Benzoic acid(BA)

One of the major factors that affects solubility is temperature. In general, the solution process will absorb energy and the solubility will increase as the temperature increase, but the solubility will decrease in increment of temperature if the solution process releases energy. Figure 3 (a, b, c) shows the exact trend of the solubility where solubility increase as the temperature increase until 90°C.



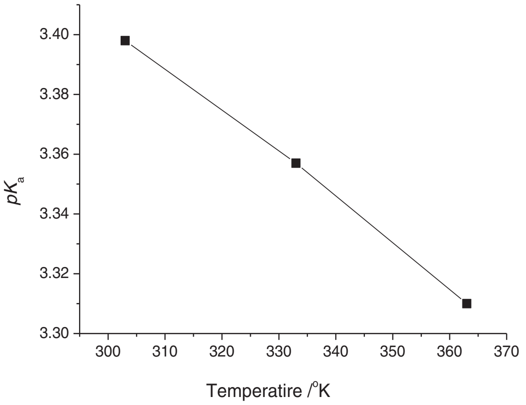
(a) (b)

Figure 3: Effect of Temperature on the solubility of benzoic acid (a) For 0% to 40% Glycerol (b) 50% to 90%Glycerol

The dissociation of benzoic acid for different percent of glycerol at 30°C, 60°C and 90°C was evaluated by repeating the procedure, and predicting the pH of each solution. $K_c$value for each percent glycerol solution at each temperature was calculated using thesame method to get thermodynamic dissociation constants (pK_a) using the plots of $\log Kc$ versus I. Figure 4 demonstrate the relation between the calculated pK_a values and temperature used. The relation between the values of $pK_a$and temperature (between 30°C and 90°C) are directly proportional. Linear form of thermodynamic equation (Van't Hoff equation) can be used to find ΔH andΔS of the benzoic acid dissociation at temperature between 30°C and 90°C:

$$logK_a = \frac{-\Delta H}{2.303R}\frac{1}{T} + \frac{\Delta S}{R} \quad (3)$$

In the equation (3), R is the universal gas constant (8.314 J·K^{-1}·mol^{-1}), and ΔH and ΔS are independent on temperature because of infinitesimal change of temperature. A linear plot of $\log K_a$ versus 1/T (Figure 5) gives thermodynamics parameters such as ΔH andΔS of dissociation of BA (benzoic acid) for different percent of glycerol as co-solvent [10]. The dissociation enthalpy and entropy change are 2.907 kJ/mol and -24.09 J/mol, respectively. Since the process changes the state of benzoic acid from solid to liquid, theentropy of the process is negative.



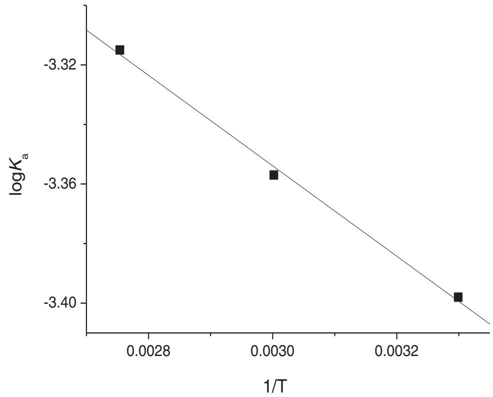


Figure 4: A plot of Van't Hoff equation Figure 5: The effect of temperature of the value of K_a

Gibbs free energy (ΔG_o) was estimatedusing the following relation:

$$\Delta G_o = \Delta H_o - T\Delta S_o \quad (4)$$

Gibbs free energies at 30°C, 60°C and 90°C are -4.390 KJ/mol, -5.114 KJ/mol and 5.837 KJ/mol respectively. Dissociation of benzoic acid decreases as the temperature increases that reduces the value of pK_a. The dissociation of benzoic acid is exothermic and spontaneous in the range of temperature of 30 - 90°C. The effect of temperature on benzoic acid dissociation under glycerol co-solvent is due to the polarity effect which results inductance inside the molecules [11]. As the temperature increase, the overall change of Gibbs free energy become more negative, thus causing spontaneity of reaction to increase. As a result, solubility increases with temperature increase.

4. Conclusion

The solubility of benzoic acid in glycerol co-solvent increases with anincrement of the glycerol concentration which corresponds that the co-solvent of glycerol enhanced the solubility of the benzoic acid. There is no regular trend of thermodynamics dissociation constant of benzoic acid in the range of temperature between 30°C to 90°C. Benzoic acid (BA) dissociation in glycerol co-solvent is spontaneous above the temperature 30°C since the Gibbs free energy are negative.

Acknowledgements

Authors would like to thanks, University Technology for providing financial support and laboratory facilities for this study.

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